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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/905,293	08/01/1997	MAE JOANNE ROSOK	030436.46SU1	5228

23914 7590 06/02/2004

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/905,293	ROSOK ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 3.15.04

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-52* ~~is~~/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-22 and 28-31* ~~is~~/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *121503*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 03/15/04 has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 11/12/03 in response to the final Office Action mailed 05/12/03.

Status of Claims

3) Claims 1-6, 8-22 and 28-31 have been amended via the amendment filed 11/12/03.

Claim 7 has been canceled via the amendment filed 11/12/03.

Claims 1-6 and 8-52 are pending in the instant application.

Claims 1-6, 8-22 and 28-31 are under examination.

Information Disclosure Statement

4) Acknowledgment is made of Applicants' Information Disclosure Statement filed 12/15/03. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Prior Citation of Title 35 Sections

5) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

6) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Maintained

7) The objection to the drawings made in paragraph 6 of the Office Action mailed 08/14/02 (paper no. 29) is maintained for reasons set forth therein.

Specification - Informalities

8) The specification is objected to for the following reason(s):

(a) The sequence of Figure 14 flows into multiple pages or panels. Each panel or page of the drawing should be labeled and referred to as Figure 14A, 14B, 14C etc. Under the section 'Brief Description of the Figures' on page 6 of the specification, Figure 14 should be referred to as such. All references to the Figures in the specification should be amended to reflect these changes in numbering.

(b) The drawings for Figure 19 are labeled as Figure 19A through 19N. However, the brief description for Figure 19 on page 6 of the specification does not refer to these as --Figure 19A through 19N--.

(c) The drawings for Figure 18 are labeled as Figure 18A through18F. However, the brief description for Figure 18 on page 6 of the specification does not refer to these as --Figure 18A through 18F--.

Rejection(s) Withdrawn

9) The rejection of claims 1-6, 8-22 and 28-31 made in paragraph 14 of the Office Action mailed 08/14/02 (paper no. 29) and maintained in paragraph 14 of the Office Action mailed 05/12/03 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn in light of Applicants' amendments to the claims and/or the base claims.

10) The rejection of claims 1, 2, 5 and 8-10 made in paragraph 16 of the Office Action mailed 05/12/03 under 35 U.S.C. § 102(b) as being anticipated by Morgan *et al.* (WO 94/29351, already of record), is withdrawn in light of Applicants' amendments to the claims and/or the base claims.

Rejection(s) Maintained

11) The rejection of claims 1-6, 8, 11, 13-15, 17-19, 21, 22 and 28-31 made in paragraph 17 of the Office Action mailed 05/12/03 under 35 U.S.C. § 102(e) as being anticipated by Yelton *et al.* (US 5,792,456, already of record), is maintained for reasons set forth therein and herebelow. See paragraph 17 of the Office Action mailed 05/12/03 for the detailed rejection.

Applicants contend that in view of the amendments to the claims, Yelton does not teach or suggest each and every element of the claimed invention.

Applicants' statement has been carefully considered, but is non-persuasive. The amendments introduced to the base claims now include structural alteration of multiple toxicity-associated regions that 'comprise' amino acids 231-238 and 310-331 of the CH2 domain of the constant region. The CH2 domain of Yelton's mutated (i.e., structurally altered) BR96 antibody does **not** include the Fc region, and therefore this mutant BR96 Fab or $(Fab')_2$ lacking CH2 domain and therefore lacking ADCC or CDC toxic properties, meets the modified immunoglobulin molecule recited in the instant claims since it comprises deletion (i.e., structural alteration) of amino acids 231-238 and 310-331 and other regions of the CH2 domain. As set forth in detail in paragraph 17 of the Office Action mailed 05/12/03, Yelton *et al.* disclosed the *in vivo* administration of the mutant BR96 to treat human carcinoma and preclinical studies done with an immunoconjugate of the mutant BR96. Since the prior art mutant BR96 Fab used in Yelton's method qualifies as a CH2-deleted and 231-238 and 310-331-amino acid-altered immunoglobulin, the disclosure of Yelton *et al.* anticipates the instant invention. That the prior art mutant BR96 Fab or $(Fab')_2$ is not associated with immunoglobulin-induced toxicity is inherent from Yelton's disclosure because Yelton *et al.* taught that Fab molecule is devoid of CH2 domain (see lines 41-44 in column 6) and therefore structurally deleted of amino acids 231-238 and 310-331. The absence of CH2 domain in the prior art antibody inherently renders it incapable of mediating antibody-dependent cellular cytotoxicity response or activating complement. Yelton's method of administering the mutant CH2-deleted BR96 to a subject inherently serves as a method of preventing or inhibiting immunoglobulin-induced toxicity. The rejection stands.

12) The rejection of claims 1, 3, 5, 12, 16 and 20 made in paragraph 18 of the Office Action mailed 05/12/03 under 35 U.S.C. § 102(b) as being anticipated by Gundel *et al.* (WO 93/02702, already of record), is maintained for reasons set forth therein and herebelow.

Applicants contend that in view of the amendments to the claims, Gundel does not teach or suggest each and every element of the claimed invention.

Applicants' statement has been carefully considered, but is non-persuasive. As set forth in detail in paragraph 18 of the Office Action mailed 05/12/03, Gundel *et al.* disclosed a method of administering to an asthma patient Fab or F(ab)2 fragments of an antibody that binds to Lewis X antigen-containing ELAM-1 receptor. The antibody used was a humanized chimeric antibody (see

claims 1-3 and 8-11; last half of page 7 and 6). Gundel's Fab or F(ab)2 antibody fragment is viewed as the same as Applicants' CH2-deleted immunoglobulin. The prior art CH2-deleted antibody is viewed as the same as Applicants' modified immunoglobulin containing structurally altered constant regions comprising 231-238 and 310-331-amino acid-alterations or deletions. The absence of the CH2 domain in the prior art antibody inherently renders it incapable of mediating antibody-dependent cellular cytotoxicity response or activating complement. Gundel's method of administering the mutant CH2-deleted immunoglobulin to an asthma patient inherently serves as a method of preventing or inhibiting immunoglobulin-induced toxicity. The rejection stands.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

13) Claims 1-6, 8-22 and 28-31 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 1, 2, is vague, indefinite and/or inconsistent in the recitation: 'method of *preventing* immunoglobulin-induced toxicity ..... so that immunoglobulin-induced toxicity is *inhibited*' (Emphasis added). It is not understood how the limitations, 'preventing' and 'inhibiting', differ in scope.

(b) Claim 1 is vague and indefinite in the limitation: 'structurally altering multiple-toxicity associated regions in the CH_2 domain ..... said regions comprise amino acids 231-238 and amino acids 310-331 of said CH_2 domain', without reciting which SEQ ID number do these specific amino acids belong to or relative to. It is unclear whether the recited amino acids 231-238 and 310-331 are relative to the amino acid sequence of a particular CH_2 domain of a specific immunoglobulin molecule, or whether these amino acids represent the multiple toxicity-associated regions of any generic immunoglobulin molecule of any class and/or subclass.

(c) Analogous criticism applies to claims 2-6.

(d) Claims 1-6 lack proper antecedence in the second recitation: 'a subject'. Since the claims already include the earlier recitation of 'a subject', it is suggested that Applicants replace the second recitation of 'a subject' with --the subject--.

(e) Claim 8 is incorrect in the recitation 'method or claim 1 or 5'.

(f) Claim 1 is vague, indefinite and confusing in the limitation: 'altering multiple toxicity-associated regions ..... wherein said multiple toxicity-associated regions comprise amino acids 231-238 and amino acids 310-331 of said CH_2 domain'. Since the open-ended limitation 'comprise' allows the inclusion of regions or amino acids other than amino acids 231-238 and 310-331, it is unclear whether the structural alteration is effected within the regions of amino acids 231-238; amino acids 310-331; amino acids 231-238 and 310-331; or other regions 'comprised' within the multiple toxicity-associated regions that exclude amino acids 231-238 and 310-331.

(g) Analogous criticism applies to claims 2-6.

(h) Claim 6 has improper antecedence in the limitation: 'said Ig protein' (see line 2 of part b), because there is no earlier recitation in the claim of an 'Ig protein'. Part (a) of the claim recites an 'Ig fusion protein', but not an 'Ig protein'.

(i) Claims 8-10 have improper antecedence in the limitation: 'method .... claim ....5, wherein said immunoglobulin molecule'. Instant claims depend from claim 5, which recites an 'immunoglobulin', but not a 'molecule'.

(j) Claim 12 has improper antecedence in the limitation: 'method of claim 5, wherein said antibody is'. Instant claim depends from claim 5, which does not recite an 'antibody'.

(k) Claim 13 is indefinite in the recitation 'a monoclonal antibody BR96'. Since BR96 is the antibody produced by the specifically deposited hybridoma, and in order to be consistent with the claim language used in claim 21, it is suggested that Applicants delete the limitation 'a'.

(l) Analogous criticism applies to claims 14, 17 and 18.

(m) Claims 15-18 and 29 have improper antecedence in the limitation: 'method of claim 1 ...., wherein said immunoglobulin'. Instant claims depend from claim 1, which does not recite an 'immunoglobulin', but an 'immunoglobulin molecule'.

(n) Claims 8-22 and 28-31, which depend directly or indirectly from one of claims 1-6, are also rejected as being indefinite because of the indefiniteness or vagueness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

14) Claims 1-6, 8-22 and 28-31 are rejected under 35 U.S.C § 112, first paragraph, as containing

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amended claims 1-6 now include the new limitations: structurally altered multiple toxicity-associated regions in the CH_2 domain of the constant region so that immunoglobulin-induced toxicity is inhibited in said subject, 'wherein said multiple toxicity-associated regions comprise amino acids 231-238 and amino acids 310-331 of said CH_2 domain'. However, there appears to be no descriptive support in the specification, as originally filed, for these added limitations. Lines 7-13 of page 10 of the specification describe the following, which do not support the instantly added limitations:

> As used herein the terms "multiple toxicity associated domains" means more than one discrete toxicity associated domain. As there appear to be at least two toxicity associated domains in the immunoglobulin molecule, ne roughly localized to amino acids 231-238 and another roughly localized to amino acids 310-331, an example of the structural alteration of multiple toxicity associated domains comprise the insertion, substitution or deletion of amino acid residues in both of these domains.

The above-cited passage describes 'multiple toxicity associated domains' as opposed to 'multiple toxicity associated regions' and completely lacks the recitation of a CH_2 domain. Therefore, the above-identified new limitations in the instant claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claim(s).

15) Claims 1-6, 8-12, 15, 16, 19, 20 and 28-31 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a method of preventing immunoglobulin-induced GI toxicity or gastroenteropathy, in animals such as dogs, comprising administering the CH_2-deleted BR96 IgG_3 monoclonal antibody, cBR96-A, said antibody produced by deleting the CH_2 domain of the constant region of the BR96 antibody, does not reasonably provide enablement for a method of preventing immunoglobulin-induced toxicity in any human or non-human subject comprising administering an immunoglobulin of any class or subclass (other than

IgG_3), as claimed currently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant application, Example 3 shows that a CH_2-domain containing BR96 IgG antibody is associated with the induction of acute gastroenteropathy when administered to dogs and that a BR96 IgG antibody which is deleted of the CH_2 domain does not cause acute gastroenteropathy in dogs to whom it has been administered. Outside this scope, however, the disclosure is not enabling for a method for preventing immunoglobulin-induced toxicity in any subject, human or non-human, comprising administering to the subject an immunoglobulin of any other Ig class or subclass having one or more mutations in the multiple toxicity-associated regions comprising amino acids 231-238 and 310-331 in its CH_2 domain, as recited broadly. The description on page 7 of the specification, for example, describes the production of the BR96 monoclonal antibody having mutations at positions 235 and 237 (hBR96-2B); the BR96 antibody having mutations at positions 318, 320 and 32 (hBR96-2C); the BR96 antibody having a mutation at position 331 (hBR96-2D); and the BR96 antibody having mutations at positions 235, 237, 318, 320, 322 and 331 (hBR96-2H). There is no evidence that these modified BR96 immunoglobulins, structurally altered as described, were administered to any human or non-human subject in whom they prevented immunoglobulin-induced toxicity. Furthermore, there is neither any evidence showing that identical mutations, if carried out in any immunoglobulin of any class or subclass other than

BR96, at one or more of the recited positions in the range of 231-238 and 310-331 of the CH_2-domain, would result in a modified immunoglobulin that would prevent immunoglobulin-induced toxicity on administration to a subject, nor is such a preventative effect predictably obtained with any immunoglobulin. From the instant specification, it appears that the recited amino acid positions 231-238 and 310-331 are relative exclusively to the BR96 monoclonal antibody. Mutations in one or more amino acids in the regions of 231-238 and 310-331 of the CH_2-domain of any other immunoglobulin of any other Ig class or subclass are unlikely to yield similar immunoglobulin-induced toxicity-preventing effect *in vitro* or *in vivo*. No evidence is of record showing that any other immunoglobulin other than the CH_2-deleted BR96 is indeed administered to a subject. There is neither a disclosure, nor any guarantee that if one administered to a subject a non-BR96 antibody of any other class or subclass having one or more mutations within the recited regions at positions 231-238 and 310-331 of the CH_2-domain, the resultant administration would automatically prevent immunoglobulin-induced toxicity in the subject. No *in vivo* data, or correlative *in vitro* data are provided in the instant application which show that the claimed method is operable with an immunoglobulin of any class/subclass having the recited structural alterations in the recited regions of the CH_2-domain. The immunoglobulin-induced toxicity-preventing effect cannot be predictably produced by the recited structural alterations in an immunoglobulin of any class/subclass, but requires a concrete demonstration of such a preventative effect in an acceptable *in vivo* animal model, or via *in vitro* experiments that are recognized in the art to correlate with the recited preventative effects. The instant specification lacks enabling disclosure in this regard. The full scope of the claims is not commensurate with the enabling disclosure. Due to the lack of specific disclosure and/or guidance, the lack of working examples enabling the full scope, the breadth of the instant claims, the unpredictability factor, and the quantity of experimentation necessary, undue experimentation would have been required at the time of the effective filing date of the instant application for one of ordinary skill in the art to reproducibly practice the full scope of the claimed method. The ability to reproducibly practice the full scope of the claimed method is well outside the realm of routine experimentation. The enablement (scope) provisions of 35 U.S.C. § 112, first paragraph, are not met and the claims are viewed as non-enabled with respect to their scope.

Rejection(s) under 35 U.S.C. § 102

16) Claims 1, 9 and 10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Suzuki *et al.* (JP 403128330A).

Suzuki *et al.* disclosed a method of administering to a subject a Fab fragment (i.e., modified or structurally altered) IgA or IgM antibody produced by removing Fc portion therefrom (see English abstract). Suzuki's Fab antibody fragment is viewed as the same as the Applicants' structurally altered IgA or IgM. The prior art CH2-deleted IgA or IgM is viewed as the same as Applicants' IgA or IgM containing structurally altered constant regions comprising 231-238 and 310-331-amino acid-alterations or deletions. The absence of the CH2 domain in the prior art Fab inherently renders it incapable of mediating antibody-dependent cellular cytotoxicity response or activating complement. Suzuki's method of administering the Fab to a subject inherently serves as a method of preventing or inhibiting immunoglobulin-induced toxicity.

Claims 1, 9 and 10 are anticipated by Suzuki *et al.*

Relevant Prior Art

17) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Siegall *et al.* (*Bioconjugate Chem.* 3: 302-307, 1992) disclosed chiBR96 Fab' and F(ab')2 immunoconjugates and their modulation and internalization (see entire document).

Remarks

18) Claims 1-6, 8-22 and 28-31 stand rejected.

19) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

20) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can

normally be reached on Monday to Friday from 7.45 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

June, 2004

S. DEVI, PH.D
PRIMARY EXAMINER